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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/382,622	08/25/99	DEES H	PHO-107-DIV

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EDWARD D MANZO
COOK ALEX MCFARRON MANZO CUMMINGS
& MEHLER LTD
200 WEST ADAMS STREET SUITE 2850
CHICAGO IL 60606

EXAMINER	
GABEL, G	
ART UNIT	**PAPER NUMBER**
1641	11

DATE MAILED: 02/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/382,622	DEES ET AL.	
	Examiner	Art Unit	
	Gailene R. Gabel	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☒ Responsive to communication(s) filed on *14 December 2000* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-16,18-20,23,25-27,50-52 and 54-59* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,12-16,18-20,23,25-27,50-52 and 54-59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

14) ☐ Notice of References Cited (PTO-892)
15) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
16) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9,10* .
17) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
18) ☐ Notice of Informal Patent Application (PTO-152)
19) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's amendment and response filed 12/4/00 in Paper No. 8 is acknowledged and has been entered. Claims 1-10, 12-16, 18-20, 23, 25-27, and 51-52 have been amended. Claims 11, 17, 21-22, 24, and 28-30 have been cancelled. Claims 54-59 have been added. Accordingly, claims 1-10, 12-16, 18-20, 23, 25-27, 50-52, and 54-59 are pending and under examination.

Priority

2. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application in the first sentence of the specification (37 CFR 1.78) including the status of the parent application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. The rejection of claims 11, 17, 21-22, 24, and 28-30 under 35 U.S.C. 112, second paragraph, is now moot in light of Applicant's cancellation of the claims.

4. Claims 15-16, 23, 25-27, and 54 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 has improper antecedent support in reciting "to biologically sensitive structures". Change to "to the to biologically sensitive structures" for proper antecedent basis.

Claim 16 has improper antecedent support in reciting "into biologically sensitive structures". Change to "into the to biologically sensitive structures" for proper antecedent basis.

Claim 16 lacks clear, distinct, sufficient, and consistent antecedent support in reciting "said targeting". Change to "said biological targeting" for proper, sufficient and consistent antecedent support.

Claim 23 has improper antecedent support in reciting "into biologically sensitive structures". Change to "into the to biologically sensitive structures" for proper antecedent basis.

Claim 23 lacks clear, distinct, sufficient, and consistent antecedent support in reciting "said targeting". Change to "said chemical targeting" for proper, sufficient and consistent antecedent support.

Claim 54 is vague and indefinite in reciting "at least one moiety at positions R^1 and R^{2}" because claim 12 to which it depends from does not recite a structure to make reference to. Accordingly, claim 54 lacks antecedent support.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. The rejection of claims 11, 17, 21-22, 24, and 28-30 under 35 U.S.C. 112, first paragraph, is now moot in light of Applicant's cancellation of the claims.

6. In light of Applicant's amendment and arguments, the rejection of claims 1-10, 12-16, 18-20, 23, 25-27, and 50-52 under 35 U.S.C. 112, first paragraph, is hereby, withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. The rejection of claims 11, 17, 21-22, 24, and 28-30 under 35 U.S.C. 102(b), is now moot in light of Applicant's cancellation of the claims.

8. Claims 1-3, 5-8, and 12-13 stand rejected under 35 U.S.C. 102(b) as being inherently anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975) for reasons of record.

Additionally, new claims 58-59 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975).

Serafini et al. has been discussed in Paper No. 7.

9. In light of Applicant's amendment and arguments, the rejection of claims 10, 15-16, 23, and 51 under 35 U.S.C. 102(b) as being anticipated by Serafini et al. (Journal of Nuclear Medicine, 1975) is, hereby, withdrawn.

10. Claims 1-3, 5-9, and 12-13 stand rejected under 35 U.S.C. 102(b) as being inherently anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) for reasons of record.

Additionally, new claims 58-59 are rejected under 35 U.S.C. 102(b) as being inherently anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)).

Neckers et al. has discussed in Paper No. 7.

11. In light of Applicant's amendment and arguments, the rejection of claims 10, 15-16, 23, and 51 under 35 U.S.C. 102(b) as being anticipated by Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) is, hereby, withdrawn.

12. In light of Applicant's amendment and arguments, the rejection of claims 12-16, 23, and 52 under 35 U.S.C. 102(b) as being anticipated by Norman et al., Invest Radiol, 26: S120-S121 (1991) is, hereby, withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. The rejection of claims 11, 17, 21-22, and 24 under 35 U.S.C. 103(a), is now moot in light of Applicant's cancellation of the claims.

14. In light of Applicant's amendment and arguments, the rejection of claims 18 and 25 under 35 U.S.C. 103(a) as being unpatentable over Norman et al. (Invest Radiol, 26: S120-S121, 1991) in view of Khaw et al. (US 5,780,052) is, hereby, withdrawn.

15. Claims 4, 14, and 18-20, 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Khaw et al. (US 5,780,052) for reasons of record.

Additionally, claims 15-16, 23, and new claims 54-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Khaw et al. (US 5,780,052).

Serafini et al., Neckers and Khaw et al. have been discussed in Paper No. 7.

New Grounds of Rejection

16. Claim 10, 51, 52, and new claims 56-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Serafini et al. (Journal of Nuclear Medicine, 1975) or Neckers D. (Journal of Photochemistry and Photobiology, A: Chemistry 47: 1-29 (1989)) in view of Norman et al. (Invest Radiol, 26: S120-S121, 1991).

Serafini et al. and Neckers have been discussed in Paper No. 7. Serafini et al. and Neckers fail to teach activating the radiosensitizer agents with ionizing radiation at greater than or equal to 1 keV and less than or equal to 1000 MeV.

Norman et al. has been discussed in Paper No. 7.

Specifically, Norman et al. teach a radiosensitizer agent such as iodinated contrast media or gandolinium for treatment of diseased tissue using ionizing radiation wherein doses absorbed from diagnostic X-rays are enhanced. Norman et al. specifically teach that the radiosensitizer agent exhibits preference to biologically sensitive diseased tumor tissues. Figure 1 shows a plot of the DEF as a function of the iodine concentration in a lymphocyte medium during irradiation at 140 kVp.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to substitute Rose Bengal taught by Serafini and Neckers for the iodinated contrast agent taught by Norman because Serafini and Neckers specifically taught application of Rose Bengal into specific tissue for use as contrast or imaging agents and Norman specifically taught that halogenation or iodination of contrast media such as gandolinium or Rose Bengal such as taught by Serafini or Neckers can be activated by ionizing radiation for concentration and treatment of diseased tissue. One or ordinary skill in the art at the time of the instant invention would have been motivated to substitute the contrast media taught by Norman with the Rose Bengal of Serafini and Neckers because of the comparable and equivalent inherent characteristic preference of Rose Bengal towards biologically sensitive diseased tumor tissues that is, likewise, exhibited resulting from halogenation or iodination upon exposure with ionizing radiation.

Response to Arguments

17. Applicant's arguments filed 12/4/00 have been fully considered but they are not persuasive.

a) Applicant argues that Serafini et al. does not teach or suggest the agent of the claimed invention as a radiosensitizer agent for use with radiosensitization or ionizing radiation in the treatment of cancer or tumors.

In response, Serafini et al., indeed, teach rose bengal, a halogenated or iodinated xanthene, which is principally tetrachlorotetraiodofluorescein, which has an inherent capacity to rapidly and efficiently concentrate into cellular molecules upon exposure to ionizing radiation; thus, a radiosensitizer or a pharmaceutical agent which in combination with ionizing radiation, finds use in treating diseased tissue with overall reduction in radiation exposure to treat diseases such as cancer or tumor. Specifically, Applicant claims a radiosensitizer agent, halogenated xanthene, a known product clearly taught by Serafini et al. and which has the inherent property to concentrate into diseased tissue (as shown by Serafini et al.). Therefore, the product of the present invention is concluded to be inherently anticipated by Serafini et al.

b) Applicant argues that Neckers et al. teaches the properties of Rose Bengal as a halogenated xanthene but does not teach or suggest the interaction of the agent with ionizing radiation or use of the agent upon interaction with ionizing radiation for treatment of cancer or tumors. Applicant further argues that interaction of the agent with ionizing radiation is affected only by absolute halogen content; the activation of the agent with visible light is fundamentally different from its activation with ionizing radiation; and its conceptual role is to serve as vehicle for concentration and delivery of active halogens.

In response, Neckers, indeed, teach rose bengal, a halogenated or iodinated xanthene, which is principally tetrachlorotetraiodofluorescein, which has an inherent

capacity to rapidly and efficiently concentrate into cellular molecules upon exposure to ionizing radiation; thus, a radiosensitizer or a pharmaceutical agent which in combination with ionizing radiation, finds use in treating diseased tissue. Specifically, Applicant claims a radiosensitizer agent, halogenated xanthene, a known product clearly taught by Neckers and which has the inherent property to concentrate into diseased tissue. Therefore, the product of the present invention is concluded to be inherently anticipated by Neckers.

In response to applicant's argument that Neckers fails to show certain features of applicant's invention, it is noted that the features upon which applicant relies, i.e. "interaction/activation of the agent with/by ionizing radiation", "interaction is affected only by absolute halogen content", are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

c) Applicant argues that Serafini et al. and Neckers fail to disclose the radiosensitizer as disclosed in the claimed invention, particularly "a radiosensitizer for treatment of cancer and tumors using radiosensitization or ionizing radiation" and Khaw et al. only disclose immunoliposomes for targeted delivery of their contents such as contrast agents to various immunologic targets.

In response to applicant's piecemeal analysis and arguments against Serafini, Neckers, and Khaw individually, one cannot show nonobviousness by attacking the references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Refer to a) and b) supra for discussion of the relevancy of Serafini and Neckers.

In this case, it would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the Rose Bengal taught by Serafini or Neckers into the immunoliposomes for target delivery taught by Khaw because Khaw specifically taught that any antineoplastic, contrast, and other pharmacologically active agents can be substituted into the immunoliposomes for use in targeting the elements into desired biologically sensitive specific tissues to allow diagnosis, localization, and therapy and Serafini and Neckers taught application of Rose Bengal into specific tissue as contrast agents. One of ordinary skill in the art at the time of the instant invention would have been motivated to incorporate the teachings of Serafini or Neckers into the immunoliposomes of Khaw because of the multifunctional capacity as achieved in combining treatment and imaging capability in using a single radiosensitization agent for treatment of cancer or tumorous tissues.

18. Accordingly, no claims are allowed.

19. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gail Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday from 7:00 AM to 4:30 PM. The examiner can also be reached on alternate Fridays from 7:00 AM to 3:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 308-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

2/23/01

Gail Gabel
Patent Examiner
Group 1641

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

02/26/01